SOCIÉTÉ CHIMIQUE DE GENÈVE

Moving Proteins Interacting With Small Molecular Weight Organic Molecules: Challenges and Opportunities for Medicinal Chemistry

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Protein tyrosine kinases catalyze the transfer of the γ-phosphate group of ATP to the hydroxyl group of tyrosine belonging to proteins substrates. Physiologically, they are involved in many signaling pathways controlling cell division, apoptosis and cell adhesion. Their activity is normally tightly regulated. Genetic modifications such as mutations, chromosomal translocations lead to deregulated protein kinase activity that is directly and in some cases even causatively linked to diseases such as cancer.

To perform their biochemical reaction protein tyrosine kinases undergo major conformational changes going from a catalytically incompetent “Off-state” to the catalytically competent “On-state” conformation.

In this talk I will present research results combining biochemistry with medicinal chemistry and computational chemistry addressing the following questions:

- Which amino acids are determining the conformational plasticity and the equilibrium between Off- and On-State?
- Which conformation should be targeted by medicinal chemists for developing protein tyrosine kinase inhibitors?

The talk will end with the presentation of the results of the development of protein tyrosine kinase inhibitors targeting the anaplastic lymphoma kinase (ALK) kinase domain of oncogenic fusion proteins containing ALK such as Npm-ALK which are linked to several cancers *e.g.* anaplastic large cell lymphoma (ALCL), neuroblastoma and non-small-cell lung cancer.

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